Incomplete Systemic Lupus Erythematosus

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Published in:
ARTHRITIS CARE & RESEARCH

DOI:
10.1002/acr.23894

Publication date:
2020

Arthritis Care & Research
Vol. 72, No. 5, May 2020, pp 607–614
DOI 10.1002/acr.23894

American College of Rheumatology
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REVIEW

Incomplete Systemic Lupus Erythematosus: What Remains After Application of American College of Rheumatology and Systemic Lupus International Collaborating Clinics Criteria?

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Incomplete systemic lupus (iSLE) is an acknowledged condition of patients with clinical signs of lupus who do not fulfill classification criteria for SLE. Some patients with iSLE have persistent mild disease, but others have serious organ involvement, and up to 55% progress to established SLE. Research on this subject could reveal predictive or diagnostic biomarkers for SLE. Ideally, it would become possible to discern those patients with critical organ involvement or a high risk for progression to SLE. This high-risk group might benefit from early treatment, which would preferably be confirmed in randomized controlled trials. This process would, however, require agreement on a definition of iSLE. The Systemic Lupus International Collaborating Clinics (SLICC) classification criteria was composed in order to diagnose SLE earlier. The present review outlines the clinical characteristics of iSLE after introduction of SLICC criteria and furthermore proposes a definition of iSLE with the aim of discriminating the high-risk group from those with a lower risk.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by formation of antinuclear autoantibodies (ANAs) and is known to have a wide range of clinical features (1). The judgment of experienced physicians is generally accepted as the gold standard for the diagnosis of SLE; however, especially for research aims, accurate disease classification is important to create comparable, consistent study groups. For that purpose, the American College of Rheumatology (ACR) criteria for SLE were proposed (2,3). A patient is classified as having SLE when 4 of 11 cumulative clinical and immunologic ACR criteria are met (Table 1) (3). In order to increase sensitivity, the Systemic Lupus International Collaborating Clinics (SLICC) more recently composed new criteria that were validated in 2012 (4) (Table 1). The most important differences between the ACR 1997 criteria and the SLICC 2012 criteria include the merging of criteria for subacute or acute cutaneous lupus and photosensitivity and addition of alternative forms of chronic cutaneous lupus; the addition of nonscarring alopecia as a clinical criterion; the redefinition of arthritis; the redefinition of the hematologic criteria; the separation and extension of immunologic criteria; the allowance of biopsy-confirmed lupus nephritis in the presence of ANAs or anti–double-stranded DNA (anti-dsDNA) to be sufficient for classification of SLE; and the requirement of at least 1 immunologic and 1 clinical criterion for SLE classification. Currently, new classification criteria for SLE are under review by a ACR/European League Against Rheumatism (EULAR) collaboration (5).

Some patients with lupus symptoms still do not fulfill any of the current classification criteria for SLE. For example, some patients could have cutaneous lupus and detectable autoantibodies but lack other features. Some patients have gradual disease onset and over time develop serious organ involvement, while others continue to have milder manifestations of the disease. Several terms have been used to qualify this heterogeneous group. The term "undifferentiated connective tissue disease" (UCTD) is used if autoimmunity features do not resemble 1 specific autoimmune disease. However, when patients have typical features of SLE without fulfilling the classification criteria, the terms "latent lupus," "early lupus," "potential lupus," "incomplete lupus," and "incomplete SLE" have all been used (6). The terms "latent lupus" and "early lupus" suggest that there will be progression to SLE, while this is not necessarily the case. "Potential lupus" could be an accurate term in reference to some patients,

Supported by the Dutch Arthritis Foundation.
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No potential conflicts of interest relevant to this article were reported.

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Submitted for publication July 17, 2018; accepted in revised form March 26, 2019.

Table 1. Overview of ACR 1997 criteria and SLICC 2012 classification criteria for SLE*

	Clinical criteria	Immunologic criteria
ACR 1997 criteria†	Malar rash Discoid rash Photosensitivity Oral ulcera Arthritis Serositis Renal involvement Neurologic involvement Hematologic manifestations	Anti-dsDNA, anti-Sm, or anti-phospholipid antibodies ANA
SLICC 2012 criteria‡	Acute or subacute cutaneous lupus Chronic cutaneous lupus Oral or nasal ulcera Alopecia Synovitis Serositis Renal involvement Neurologic involvement Hematologic manifestations	ANA Anti-dsDNA Anti-Sm Antiphospholipid antibodies Low complement Positive Coombs' test

* ACR = American College of Rheumatology; SLICC = Systemic Lupus International Collaborating Clinics; SLE = systemic lupus erythematosus; anti-dsDNA = anti–double-stranded DNA; ANA = antinuclear antibodies.
† Patients were classified as having SLE when 4 of the 11 criteria were met.
‡ Patients were classified as having SLE if 4 criteria with at least 1 clinical and 1 immunologic or biopsy-proven lupus nephritis and ANA or anti-dsDNA were met.

but for patients with a clear form of lupus (for example, cutaneous lupus), this label would not be appropriate, as they would already have lupus of the skin. We decided to use the term "incomplete SLE" (iSLE), as this can include both stable mild disease as well as more severe disease that is still not classifiable as SLE.

Investigating iSLE is of significant relevance, as it could reveal immunologic changes that occur when the disease progresses to SLE. Furthermore, longitudinal follow-up of these patients potentially reveals predictive biomarkers that enable stratification of the risk for progression to established SLE. This investigation of iSLE would improve patient care by allowing high-risk patients to be followed up more intensively and to possibly start treatment earlier; low-risk patients could be exempted from intensive follow-up and be reassured about disease progression. Additionally, patients with iSLE might benefit from inclusion in clinical trials. However, because patients with iSLE are probably an even more heterogeneous group than those with SLE, a consensus definition is of great importance for future research.

In the present review, the characteristics of iSLE before and after introduction of SLICC criteria are outlined. Moreover, clinical and serologic risk factors are described in order to ultimately better define this patient group, especially those patients at high risk of progression to SLE or severe organ involvement.

Characteristics of iSLE and risk factors for progression to SLE

Throughout the past decades, a number of studies investigating iSLE have been published. Most publications on iSLE are based on patients with clinical features of SLE who do not fulfill ACR criteria (3), and only some studies use the SLICC criteria. Table 2 shows an overview of these studies (7–20).

The most commonly occurring features in these patients are mucocutaneous symptoms (up to 46%), arthritis (up to 53%), and hematologic disorders (up to 52%). A significant number of patients with iSLE, however, have serious organ involvement. Up to 36% of patients with iSLE have serositis, up to 27% have renal involvement, and up to 6% have neurologic symptoms. Moreover, 53% of hospitalized iSLE patients have been found to have increased disease damage scores, and in 1 cohort, lupus-associated mortality in patients with iSLE was equal to that in those with SLE (15). Progression to SLE occurs in 5–57% of patients with iSLE within 1–10 years.

Seven studies have reported the progression rate to SLE, each of which are discussed herein. In the first study, by Greer and Panush (7), 38 patients with iSLE who were defined as meeting ≥2 but <4 of the ACR criteria (2) were retrospectively compared to 42 patients with SLE. At inclusion, the median disease duration of the iSLE group was 38 months, and the mean time of consecutive follow-up was 19 months. Compared to patients with iSLE, patients with SLE presented more frequently with malar rash, hematologic features, and organ involvement, whereas discoid rash occurred more often in patients with iSLE. Only 5% of patients (n = 2) developed definite SLE (1 patient at 9 months and 1 patient at 26 months after the first presentation); however, the characterisics of these patients were not published by the authors. At the end of follow-up of the remaining patients with iSLE, 11% were not classified as having a connective tissue disease, 26% had discoid lupus erythematosus, 5% subacute cutaneous lupus erythematosus, and 53% continued to have iSLE.

The second study was a prospective study conducted in Puerto Rico (9), in which 87 patients with iSLE were followed up for a mean of 2.2 years. These iSLE patients were defined as having met ≥1 but <4 criteria according to the ACR criteria for SLE (2)

Table 2. Overview of present studies concerning incomplete SLE*

Study author, year (ref.)	Definition of iSLE	Patients with iSLE, no.	Female, %	Mean age, years	Disease duration at baseline, years	Clinical features of patients (%)	Serology of patients (%)	Follow-up	Progression to SLE	Predictors for progression to SLE
Greer and Panush, 1989 (7)	2–3 ACR 1997 criteria	38	87	37	3.2	Arthritis (47) Discoid rash (34) Photosensitivity (24) Hematologic (18) Serositis (16) Neurologic (3)	ANA (82) Anti-dsDNA (0)	1.6 years (mean)	2 patients (5%)	NA
Calvo-Alén et al, 1995 (8)	Clinical diagnosis SLE, <4 ACR 1997 criteria	22	87	47	2.3	Mucocutaneous (45) Serositis (36) Renal (27) Arthritis (27) Lymphopenia (23)	ANA (95) Anti-dsDNA (22)	NA	NA	NA
Vilá et al, 2000 (9)	1–3 ACR 1997 criteria	79	94	30	4.4	Photosensitivity (25) Lymphopenia (23) Malar rash (11) Arthritis (11) Discoid rash (6) Renal (1)	ANA (97) Anti-Ro/SSA (8) Anti-dsDNA (4)	2.2 years (mean)	9% after mean 4.4 years ± 4 years	Younger age (24.5 vs. 34 years) Photosensitivity Anti-dsDNA Low C3
Swaak et al, 2000 (10)	1 organ system and ANA and clinical suspicion of SLE	100	99	40	4.5	Leucopenia (36) Arthritis (15) Renal (11) Malar rash (4) Discoid rash (4) Pericarditis (4)	ANA (100)	3 years	3% after 3 years	Not shown
Ståhl Hallengren et al, 2004 (11)	4 ACR criteria and 1 organ system	28	93	45	NA	Malar rash (25) Arthritis (32) Renal (18) Hematologic (14) Serositis (14) Discoid rash (7)	ANA (100)	13 years (median, range 10–20 years)	57% after median 5.3 years	Malar rash aCL
Laustrup et al, 2010 (12)	Clinical diagnosis SLE, <4 ACR 1997 criteria	26	Not available	Not available	NA	Photosensitivity (46) Arthritis (31) Hematologic (31) Malar rash (19) Serositis (19) Renal (15) Neurologic (4)	ANA (100)	8 years	27%	None identified
Olsen et al, 2012 (13)	2–3 ACR 1997 criteria	22	86	49	Not available	Photosensitivity (27) Arthritis (23) Hematologic (18) Serositis (9)	ANA (95) Anti-Ro/SSA (9) Anti-dsDNA (14) Anti-Sm (5)	10 years	14% after mean 3.8 years	Younger age; high overall IgG-autoreactivity; high IgM anti-Ro/SSA and IgM Anti-LA/SSB
Al Daabil et al, 2014 (14)	1–3 ACR 1997 criteria	264	94	39	Not available	Arthritis (53) Malar rash (14) Renal (2) Discoid rash (1)	ANA (88) Anti-dsDNA (17)	6.3 years	21% after 6.3 years	Oral ulcers Renal involvement Anti-dsDNA
Chen et al, 2015 (15)	1–3 ACR 1997 criteria and clinically most fitting diagnosis SLE	77[3]	87	34	3.6	Hematologic (52) Arthritis (21) Serositis (21) Renal (17) Malar rash (9) Neurologic (6)	ANA (97) Anti-dsDNA (22)	NA	NA	

(Continued)

Table 2. *(Cont'd)*

Study author, year (ref.)	Definition of iSLE	Patients with iSLE, no.	Female, %	Mean age, years	Disease duration at baseline, years	Clinical features of patients (%)	Serology of patients (%)	Follow-up	Progression to SLE	Predictors for progression to SLE
Rúa-Figueroa et al, 2015 (16)	3 ACR 1997 criteria, clinical diagnosis SLE	345	85	42.9	8.0	Arthritis (44) Hematologic (43) Photosensitivity (20) Malar rash (11) Serositis (9) Renal (4) Neurologic (1)	ANA (95)	5.6 years	NA	
Olsen et al, 2016 (17)	1–3 ACR 1997 criteria	70	94	45	Not available	Photosensitivity (23) Arthritis (16) Malar rash (20) Oral ulcers (13) Serositis (9)	ANA (97)	NA	NA	
Bortoluzzi et al, 2017 (20)	UCTD (ANA + ≥1 autoimmune symptom)	329	97	46	Not available	Malar rash (29) Leukopenia (13) Synovitis (11) Alopecia (11) Ulcers (10) Neurologic (4)	ANA (100) Low complement (14) aPL (14) Anti-dsDNA (2)	5–10 years	44 of 329 (14%) fulfilled SLICC criteria at baseline; 23 of 329 (7%) developed SLE according to SLICC	Not available
Aberle et al, 2017 (18)	Clinical diagnosis SLE, not fulfilling ACR 1997 or SLICC 2012 criteria	291	87	48	Not available	Arthritis (45) ACLE or SCLE (43) Leuko-/lymphopenia (23) Ulcers (11) CDLE (9) Serositis (6) Renal (5) Neurologic (1)	ANA (96) aPL (13) Anti-dsDNA (12)	NA	NA	
Yusof et al, 2018 (19)	ANA plus ≥1 SLICC 2012 criterion	118	88	48	Not available	Synovitis (26) ACLE or SCLE (26) Leuko-/lymphopenia (16) Ulcers (11)	ANA (100) Anti-Ro/SSA (42) Anti-dsDNA (36)	1 year	12%	1 clinical SLICC criterion at baseline; positive family history of autoimmune rheumatic disease

* SLE = systemic lupus erythematosus; ref. = reference; iSLE = incomplete systemic lupus erythematosus; ACR = American College of Rheumatology; ANA = antinuclear antibody; anti–dsDNA = anti–double-stranded DNA; NA = not applicable; aCL = anticardiolipin antibody; UCTD = undifferentiated connective tissue disease; aPL = antiphospholipid antibody; SLICC = Systemic Lupus International Collaborating Clinics; ACLE = acute cutaneous lupus erythematosus; SCLE = subacute cutaneous lupus erythematosus; CDLE = chronic discoid lupus erythematosus.

and had no classification or specific symptoms of other rheumatic diseases. Evolution of iSLE to SLE occurred in 9% of these patients, with a mean interval of 4.4 years between onset of symptoms and diagnosis. These patients in whom iSLE progressed to SLE were younger than those who remained in the iSLE group (ages 24.5 years versus 34 years), but this difference did not reach statistical significance ($P = 0.06$). In terms of clinical manifestations, the patients who developed SLE more frequently had photosensitivity, positive anti-dsDNA, and decreased C3 levels at baseline. Importantly, organ involvement was uncommon in both groups.

The third study was a multicenter study that prospectively evaluated patients with iSLE (10). For these patients, iSLE was defined as the presence of symptoms of 1 organ system, ANA positivity, and clinical suspicion of possibly developing SLE in the future. Although 122 patients were identified using this definition of iSLE, 22 already fulfilled the 1982 ACR criteria of SLE at first evaluation. Of the remaining 100 patients, 3 developed SLE during the next 2 years. Clinical symptoms consisted mainly of fatigue, arthritis, nonhemolytic anemia, and leucopenia, while organ involvement was uncommon. These findings suggest that patients with iSLE whose illness does not progress to SLE during a short term represent a milder disease entity. Unfortunately, no comparison of baseline characteristics was made between the patients who developed SLE and the remaining iSLE group.

The fourth study, by Ståhl Hallengren et al (11), included long-term prospective follow-up of 28 patients with iSLE, which was defined as ANA positivity and symptoms in ≥1 organ. After a median duration of 5.3 years, iSLE in 16 patients (57%) had progressed to SLE according to ACR criteria (2). The iSLE patients whose illness progressed to SLE were all ANA positive (as per protocol for the study), and all but 1 patient had at least 1 clinical symptom at baseline. The progressive patient who did not display clinical sympoms at baseline had a first-degree family member with SLE. All 6 of the patients who had malar rash and all 6 patients who had anticardiolipin antibodies developed established SLE.

In the fifth study, Laustrup et al (12) investigated a cohort of 26 patients with iSLE (clinical diagnosis of SLE, not meeting ACR criteria) (2). All patients had detectable ANA, and the most prevalent clinical symptoms were photosensitivity, malar rash, and hematologic disorders. In 7 of these patients (27%), iSLE transformed into SLE during 8 years of follow-up. No predictive factors could be identified.

In the penultimate study, Al Daabil et al prospectively enrolled 264 patients who fulfilled 1–3 of the ACR classification criteria for SLE (14). Throughout an average follow-up time of 6.3 years, iSLE in 21% of patients evolved to SLE. At baseline, arthritis and presence of anti-dsDNA and anti-Ro/SSA were more frequent in the group that had eventually progressed to SLE. However, after multivariable logistic regression analysis, only oral ulcers, anti-dsDNA, and symptoms of renal involvement were found to be independent risk factors for the development of SLE. During follow-up of the group that did not develop SLE, 61% remained classified as having iSLE, while 18% had another diagnosis (fibromyalgia, autoimmune thyroid disease, mixed connective tissue disease, rheumatoid arthritis, or cutaneous lupus). Importantly, the ANA positivity rate was lower (79%) in this group compared to the remaining SLE group (98%).

Finally, a recent prospective observational study by Yusof et al (19) included 118 subjects with ANA positivity (titer ≥1:80) who fulfilled ≥1 clinical SLICC criteria and had symptom duration of <12 months. Clinical symptoms included mucocutenaous, musculoskeletal, and hematologic features. During the 12 months of follow-up, 19 patients (16%) progressed to a classified connective tissue disease, of which 14 (12%) developed SLE according to SLICC criteria and 5 (4%) developed Sjögren's syndrome. Two patients developed critical organ involment, 1 with serositis and 1 with nephritis. All iSLE patients whose illness progressed to SLE had fulfilled at least 1 clinical SLICC criterion at baseline (not further specified by the authors), indicating that this was an important risk factor of disease progression. Furthermore, after logistic regression analysis, a positive family history of autoimmune rheumatic diseases was associated with a high risk of disease progression. Notably, the authors showed that interferon activity was strongly associated with progression to established SLE.

The above studies are extremely valuable in the underscoring of the variable nature of iSLE. Importantly, most of the aforementioned studies are retrospective in nature, which may result in underestimation of the progression rate. Logic would suggest that patients with a prolonged disease course are more likely to be included than those who quickly progressed to SLE. This is further supported by the fact that the 2 prospective studies (11,19) demonstrated the highest percentage of iSLE patients whose illness progressed to SLE, i.e., 12% of patients after 1 year and 57% after a median of 5.3 years. In summary, clinical symptoms and disease severity are highly variable among patients with iSLE, ranging from persistent mild disease to rapid progression to SLE and/or to critical organ involvement. In regard to clinical features, acute cutaneous lupus erythematosus, photosensitivity, serositis, ulcers, and renal involvement seem to occur more often in patients with iSLE whose illness progresses to SLE. These patients in whom iSLE progressed to SLE were younger. Furthermore, the presence of anti-dsDNA, anticardiolipin antibodies, and hypocomplementemia are all associated with progression to SLE. None of these findings, however, can accurately predict the establishment of SLE.

Consequences for iSLE classification after introduction of SLICC criteria

After the introduction of the SLICC criteria, various researchers have focused on the consequences for classification of clinically diagnosed lupus patients. A recent systematic review and meta-analysis (21) showed that for adult patients with SLE, SLICC cri-

teria increased sensitivity compared to ACR criteria (3) (94.6% versus 89.6%), while specificity decreased only slightly (95.5% versus 98.1%). Unfortunately, most studies on iSLE have noted the number of ACR criteria (3) but have not published individual patient characteristics. Therefore, for the purpose of the present review, retrospective evaluation of the consequences of applying SLICC criteria in these patient cohorts could not be performed.

Four additional studies have applied both ACR and SLICC criteria for the evalution of iSLE. In an observational study, Chen et al (15) included 77 hospitalized iSLE patients (iSLE being defined as fulfilling <4 ACR criteria [3]) in order to analyze the organ damage features of this group. The mean disease duration was 43 months, and the mean Systemic Lupus Erythematosus Disease Activity Index score was 6.6. When the authors applied SLICC criteria in this cohort, 43 patients (56%) who did not meet ACR criteria (3) were classified as having SLE. More than half of the patients (53%) had increased SLICC/ACR Damage Index scores, mostly because of pulmonary arterial hypertension, and renal and neurologic damage. Seventeen of the 41 patients (41%) with increased damage scores did not meet any of the criteria sets.

In the study by Olsen et al (17) (Table 2), none of the identified 70 patients with iSLE (which was defined as fulfilling 1–3 of the ACR criteria for SLE [3]) fulfilled the SLICC criteria for SLE classification. The authors concluded that classification using the SLICC criteria would not change the prevalence of the incomplete lupus designation.

Aberle et al (18) reviewed the medical records of 3,397 patients with a clinical diagnosis of SLE and applied both ACR criteria (3) and SLICC criteria (4) in all patients. They identified 440 subjects who only met 3 ACR criteria (3). One-third of these patients met SLICC criteria (4), resulting in 291 patients (9% of all patients with a clinical SLE diagnosis) who could not be classified by any of the criteria sets. A large proportion of these nonclassifiable patients had organ involvement (6% serositis, 5% renal involvement, and 1% neurologic features) (Table 2). The majority of these patients were being treated with hydroxychloroquine and/or steroids, and 10% required other immunosuppressive drugs.

Bortoluzzi et al (20) retrospectively selected 329 white patients with UCTD (defined as having signs and symptoms suggestive of a connective tissue disease), ANA positivity, and a disease duration of at least 1 year who did not fulfill ACR criteria (3). In retrospect, 44 patients (13%) already fulfilled the SLICC criteria (4) at baseline. The most commonly occurring clinical features in this group were acute cutaneous lupus erythematosus (55%), leukopenia (39%), and synovitis (30%). Regarding critical organ involvement, 7 patients (16%) had neurologic involvement, and 2 (5%) had serositis, while none had renal involvement. Of the remaining 285 patients with UCTD, information regarding 206 could be retrieved from 5 to 10 years follow-up. During this period, 14 patients with UCTD (5%) progressed to SLE according to ACR criteria (3), and 23 patients (8%) according to SLICC criteria (4). Unfortunately, the authors did not show the disease characteristics of these groups.

In summary, more patients were classified as fulfilling SLICC criteria than ACR criteria for SLE (3), but still ~5% of the patients with a clinical diagnosis remained unclassified, as can be expected based on sensitivity. More importantly, a considerable share of these patients had serious organ involvement or required treatment with immunosuppressive drugs and thus might benefit from inclusion in clinical trials.

Requirement of consensus definition for iSLE

Currently, researchers use various definitions for iSLE, which hinders comparability between different studies. Ideally, a classification system would include patients who are at the highest risk of developing SLE or serious organ damage and exclude those who have prolonged mild symptoms or develop other autoimmune diseases. Prospective documentation of a consistent group of patients with iSLE is required in order to better define the high-risk group and to determine predictive biomarkers. We therefore ask for the development of a consensus on the definition of iSLE in order to, ideally, combine forces and start prospective documentation of patients with iSLE.

Definition of iSLE involves a very heterogeneous group of patients and should include patients at the highest risk of developing SLE. Mucocutaneous symptoms, serositis, renal symptoms, anticardiolipin antibodies, low complement, and anti-dsDNA are all associated with progression to SLE. Table 3 shows our proposed

Table 3. Proposed definition of incomplete systemic lupus erythematosus (iSLE)*

Required
ANA at a titer ≥1:80
And ≥1 of the following criteria†
Acute or subacute cutaneous lupus
Chronic cutaneous lupus
Oral or nasal ulcers
Alopecia
Synovitis
Serositis
Neurologic manifestation
Renal manifestation
Or 2 of the following criteria
Hematologic manifestations‡
Immunologic features§
Positive family history of autoimmune rheumatic disease¶
And not meeting ACR 1997 criteria and/or SLICC 2012 criteria for SLE

* ANA = antinuclear antibody; ACR = American College of Rheumatology; SLICC = Systemic Lupus International Collaborating Clinics; SLE = systemic lupus erythematosus.
† As specified in SLICC classification criteria.
‡ As specified in SLICC classification criteria. Hematologic manifestation included hemolytic anemia or leukopenia or lymphopenia (1,000/mm^3 at least once) or thrombocytopenia (100,000/mm^3 at least once).
§ As specified in SLICC classification criteria. Immunologic features included anti–double-stranded DNA or anti-Sm or antiphospholipid antibodies or low complement or direct Coombs' test.
¶ Included first- or second-degree relative with autoimmune rheumatic disease.

definition of iSLE, which aims at including patients with a high risk of developing SLE or serious organ involvement. ANA positivity at a titer ≥1:80 should be present in order to be classified as iSLE, as this is a key feature of SLE. A recent systematic review and meta-regression (22) on the diagnostic value of ANAs reported 97.8% sensitivity and 74.7% specificity for ANA at a titer ≥1:80. Also, in an observational study (23) on 616 patients who were referred due to possible SLE, 99.5% of patients with early SLE were ANA positive. The ACR/EULAR international collaboration on development of new classification criteria for SLE has also reached consensus on using positive ANA at a titer ≥1:80 as entry criterion 5.

Furthermore, a definition of iSLE should include at least 1 clinical symptom. The study by Ståhl Hallengren et al included patients fullfilling at least 1 clinical criterion, and this group had the highest disease progression rate compared to other longitudinal studies on iSLE (11). Moreover, all patients whose illness progressed to iSLE who were included in the study by Yusof et al (19) had fulfilled a clinical criterion. We propose the usage of the clinical criteria as recorded in the SLICC criteria (see Table 1), as these criteria have been demonstrated to be more sensitive than ACR criteria (21).

In the absense of other clinical symptoms, hematologic features have been shown not to be very specific for SLE (23). Therefore, hematologic features should be accompanied by other immunologic features in order to classify iSLE. Having a first- or second-degree relative with an autoimmune disease has also been identified as a risk factor for developing SLE and should therefore be taken into account in the definition of iSLE. Although there is not much literature on this subject, we weighted this factor similarly to an immunologic or hematologic feature. Based on our review, we expect to distinguish a patient group at high risk of progressive disease by using this definition of iSLE.

In summary, there is still a need for better recognition of patients with iSLE, especially those with a high-risk profile for progression to SLE and/or development of organ damage. In the present review, an overview of the current literature was presented in order to clarify the characteristics of high-risk patients. Prospective documentation of a consistent group of patients with iSLE is necessary in order to define the high-risk group and to determine predictive biomarkers. Therefore, it is necessary to reach a widely accepted consensus on a definition for lupus patients who do not fulfill the classification criteria for SLE.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication.

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